

Predictors of survival in anuric peritoneal dialysis patients

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Background. Residual glomerular filtration rate (GFR) is a much more important determinant of survival in peritoneal dialysis patients, than peritoneal solute clearances. However, anuric peritoneal dialysis patients are solely dependent on peritoneal solute clearances. The aim of the study was to analyze the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients, and to establish the minimum levels of small solute clearances and net ultrafiltration. These objectives were investigated in a prospective cohort study in incident peritoneal dialysis patients who had become anuric during follow-up.

Methods. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective multicenter cohort study in which new adult dialysis patients are included and followed during 6 months intervals. Included were 542 peritoneal dialysis patients. Of these, 166 developed anuria, 130 of which could be included in the study.

Results. Two-year patient survival after the outset of anuria was 67%, technique survival 73%, and the combined 2-year patient and technique survival was 50%. Risk factors associated with mortality were age, comorbidity, the duration of peritoneal dialysis before anuria, and a low serum albumin. Peritoneal solute clearances were analyzed time-dependently. These parameters were not associated with survival when analyzed as continuous variables and also not when the analyses were done in quintiles, although the time-dependent approach was almost significant for Kt/V_{urea} . On the other hand, when the results were analyzed dichotomously using predefined cutoff points, $Kt/V_{urea} < 1.5$ per week and creatinine clearance < 40 L/week/1.73 m² were associated with an increase in the relative risk of death. Also peritoneal ultrafiltration was significantly associated with survival.

Conclusion. The survival of anuric peritoneal dialysis patients is in line with expectations based on the duration of dialysis. The risk factors for death are the same as in the dialysis population as a whole. Besides an association with ultrafiltration, our study enabled us to define the lower limits of adequate peritoneal

dialysis, that is $Kt/V_{urea} < 1.5$ per week and creatinine clearance < 40 L/week/1.73 m².

In several retrospective and prospective cohort studies predictors of outcome in patients treated with peritoneal dialysis have been investigated [1–17]. Age, the presence of comorbidity, systolic hypertension, poor nutritional status, and a low serum albumin concentration were the main factors related to patient survival in these studies. An effect of the removal of low-molecular-weight solutes, expressed as Kt/V_{urea} or weekly creatinine clearance was reported in most series [8–12, 14, 16, 17], but not in all of them [1, 2, 15]. However, this effect was mainly dependent on the contribution of residual glomerular filtration rate (GFR) [8, 12, 14, 16–18]. Also, no effect of peritoneal clearance on patient survival was found in a randomized controlled trial in Mexico [19]. The survival of patients without residual renal function is dependent on peritoneal clearances by definition, as a clearance of zero will lead to death. The minimum requirement is, however, unknown. Bhaskaran et al [20] performed a retrospective analysis in anuric peritoneal dialysis patients in Canada and were unable to find a significant effect of Kt/V_{urea} on the relative risk of death. Only when Kt/V_{urea} was analyzed dichotomously, that is < 1.85 or > 1.85 per week, a nonsignificant ($P = 0.1$) reduction was found in the relative risk of death. In contrast, multivariate analysis of a prospective cohort study in anuric patients in Hong Kong showed a significant effect of Kt/V_{urea} on survival [21]. The majority of these patients were treated with three 2 L exchanges per day.

Based on the equivocal results of the above studies, the aim of the present study was to analyze the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients and to establish the minimum levels of small solute clearances and ultrafiltration. These objectives were investigated in a prospective cohort study in incident peritoneal dialysis patients in The Netherlands, who had become anuric during follow-up.

Key words: peritoneal dialysis, anuria, dialysis adequacy, patient survival, technique survival.

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METHODS

Patients

All patients in this study participated in The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). This is an ongoing prospective multicenter cohort study, in which incident adult (>18 years old) chronic dialysis patients are included and followed on a regular basis (see below). Patients with previous renal replacement therapy are excluded. Assessments are done at 0 months, 3 months, 6 months, and every 6 months thereafter. No recommendations with regard to the dialysis dose are given. The cohort started in January 1997. At the first of September 2002, 1698 patients had been included in the cohort and 1489 were on dialysis after 3 months; 542 of these were treated with peritoneal dialysis. For the present analyses, peritoneal dialysis patients whose 24-hour urine production had dropped to less than 200 mL/day during follow-up were included. The first regular follow-up assessment where this condition was met was taken as baseline (onset of anuria) and used in further analyses. The NECOSAD study was approved by the committees of medical ethics of the participating hospitals and informed consent was obtained from all patients before inclusion.

Data collection

In the NECOSAD study, data are collected on demography, primary renal disease, comorbidity, laboratory investigations, nutritional status, and therapy characteristics. Primary renal disease was classified according to the codes of the European Dialysis and Transplant Association/European Renal Association (EDTA/ERA). Comorbidity at the time of development of anuria was expressed as the Davies risk score [10]. Subjective global assessment (SGA) was used as measure of the nutritional status and was performed using the method originally described by Baker et al [22], modified into a 7-point scale [11, 23]. Blood laboratory investigations included hemoglobin, serum albumin, plasma urea, and plasma creatinine. In a corresponding 24-hour dialysate collection, urea and creatinine were assessed. The urea distribution volume (V) used to calculate Kt/V_{urea} was obtained by the formulas of Watson, Watson, and Batt [24]. The dialysate/plasma (D/P) ratio of creatinine was calculated from the concentrations of creatinine in the 24-hour dialysate and the plasma. Patients were classified as fast transporters when D/P creatinine was higher than the mean value plus one standard deviation [25]. The mean of baseline (start of anuria) and follow-up values of Kt/V_{urea} , creatinine clearance, ultrafiltration volume, hemoglobin, and serum albumin were used for the analyses.

Statistics

All analyses were performed using SAS, version 8 for Windows software. Follow-up of the patients was censored at the time of transplantation, at day 60 following transfer to hemodialysis, patient withdrawal, or at September 1, 2002. If a patient died within 60 days after transfer to hemodialysis, this transfer was disregarded and his/her death was treated as an event to be attributed to peritoneal dialysis. Hence, only death occurring during or shortly after treatment with peritoneal dialysis was taken into account ("as-treated" censoring strategy). In the analysis of technique survival the event was transfer to hemodialysis and all other observations were censored. Both death and transfer to hemodialysis were events for the analysis of the combined patient and technique survival.

The effects of adequacy on patient, technique, and combined patient and technique survival were assessed in a multivariate Cox proportional hazards analysis in which important patient characteristics that are known to influence outcome were taken into account [26]. These included age, Davies comorbidity score, SGA, time on dialysis, serum albumin, and blood hemoglobin concentrations. Peritoneal Kt/V_{urea} , creatinine clearance, and ultrafiltration were entered as covariates. The analyses were done using the adequacy parameters as time-dependent covariables. That is, survival is examined in every 6 months period after the measurement of the adequacy parameters. For each parameter the last observed value prior to each 6-month interval was used. Kt/V_{urea} was included as quintiles in the Cox models for patient survival, technique survival, and the combined patient and technique survival. After correction for significant risk factors in the Cox model, the effect of Kt/V_{urea} , creatinine clearance, and ultrafiltration on patient and technique survival were subsequently also analyzed after entering them as continuous variables and dichotomized at predefined clinically relevant levels. These levels were a Kt/V_{urea} of 1.7/week and a creatinine clearance of 45 L/week/1.73 m², because these are values that are obtained in the majority of continuous ambulatory peritoneal dialysis (CAPD) patients. As we wanted to detect the lower threshold, Kt/V_{urea} of 1.5 and creatinine clearance of 40 L were also analyzed.

The statistical contribution of a categorized variable with more than two levels was evaluated by means of the confidence intervals of the estimated individual parameters and by means of an overall-test procedure (chi-square Wald statistic).

RESULTS

A urine production of less than 200 mL/day developed during follow-up in 166 of the 542 peritoneal dialysis patients present at 3 months. Of these, 130 could

Table 1. Demographic variables and comorbidity at time of anuria (N = 130) [means (SD) or %]

Time on dialysis <i>months</i>	13 (10)
Age at entry <i>years</i>	53 (17)
Gender% <i>male</i>	38
Primary kidney disease %	
Diabetes	12
Renovascular	12
Glomerulonephritis	24
Other	52
Davies score% <i>intermediate or high comorbidity</i>	45
Body mass index <i>kg/m²</i>	24.8 (4.0)
Subjective global assessment%	
≤5	27
6	28
7	45

be included in the analysis because urine production remained less than 200 mL/day during follow-up and a complete data set on adequacy and nutritional parameters was available. One hundred and two of these 130 patients were treated with CAPD, and the remaining 28 with automated peritoneal dialysis. During follow-up, 32 patients died. Causes of death were classified as cardiovascular [12], infectious [3], or various other reasons [17]. Twenty eight patients received a kidney transplant, 26 patients were transferred to hemodialysis. Reasons for transfer to hemodialysis were peritonitis [16], surgical complications [5], and membrane failure [5]. Demographic and comorbidity data of the patients at the onset of anuria are listed in Table 1. Because of the small number of patients in the subgroup with severe comorbidity, the subgroups of patients with intermediate and severe comorbidity were combined. Biochemical variables and peritoneal transport characteristics at baseline are listed in Table 2. Kaplan-Meier survival curves are shown in Figure 1. Two-year patient survival was 67%, technique survival 73%, and the combined 2-year patient and technique survival was 50%.

Multivariate Cox regression analysis revealed several factors as predictors of patient survival, technique survival, and the combined patient and technique survival (Table 3). A higher age, more comorbidity, longer stay on dialysis before onset of anuria, and low serum albumin were all significantly associated with worse patient survival. When technique survival was studied, we found a positive relationship between survival and comorbidity. That is, a high comorbidity was associated with a better technique survival. Worse nutritional status and fast or fast average peritoneal membrane transport status had a negative effect on technique survival.

The effects of peritoneal transport parameters on patient survival are listed in Table 4. These three parameters were each analyzed as continuous variable, as quintiles, and as dichotomous variables using cutoff points with clinical relevance. Ultrafiltration was significantly

Table 2. Biochemical variables and peritoneal transport characteristics at time of anuria (N = 130) [means (SD) or %]

Hemoglobin <i>g/dL</i>	11.6 (1.6)
Serum albumin <i>g/dL</i>	3.6. (0.6)
Peritoneal creatinine clearance	48.6 (10.7)
<i>L/week/1.73 m²</i>	
Peritoneal Kt/V _{urea} /week	1.8 (0.3)
Membrane transport status %	
Slow/slow average	59
Fast average/fast	41
Ultrafiltration <i>L/day</i>	1.6 (0.6)

associated with survival and creatinine clearance almost reached statistical significance. Kt/V_{urea} analyzed as a continuous variable was not associated with survival. The lowest quintiles for Kt/V_{urea}, creatinine clearance, and ultrafiltration showed an increased relative risk of death, although statistical significance was not reached. However, no dose-effect relationship was observed in the other quintiles. In further dichotomous analysis, it appeared that Kt/V_{urea} <1.5 per week and creatinine clearance <40 L/week/1.73 m² were associated with a significant increase in the relative risk of death. The cutoff points for ultrafiltration did not reach statistical significance. Because normalizing clearances for a parameter of body size has been questioned, the analyses in quintiles were also repeated for Kt and for creatinine clearance not corrected for body surface area in the time-dependent model. The overall *P* value for Kt/V_{urea} was 0.85 and 0.33 for creatinine clearance. The first was worse than for Kt/V_{urea}, while the latter was similar for creatinine clearance/1.73 m² body surface area. Also including body mass index in the multivariate models had no significant effects (data not shown).

Similar analyses as for mortality were done for technique survival, and are shown in Table 5. A tendency was present (*P* < 0.1) for an association between creatinine clearance and an increased risk of technique failure, both in the analysis in quintiles and in the one using creatinine clearance as a continuous variable. Analysis using the cutoff points showed no association. Moreover, no associations were found for Kt/V_{urea} and ultrafiltration with technique survival.

DISCUSSION

The effects of the dialysis dose on the survival of dialysis patients is best studied in those who have no or negligible residual urine production, because these patients are totally dependent on dialysis for the removal of uremic waste products, and excess of fluid. It has been shown in a randomized controlled trial in Mexico that increasing the peritoneal creatinine clearance to 60 L/week/1.73 m² had no effect on the survival of anuric patients [19]. This corresponds with an increase of Kt/V_{urea} from an average of

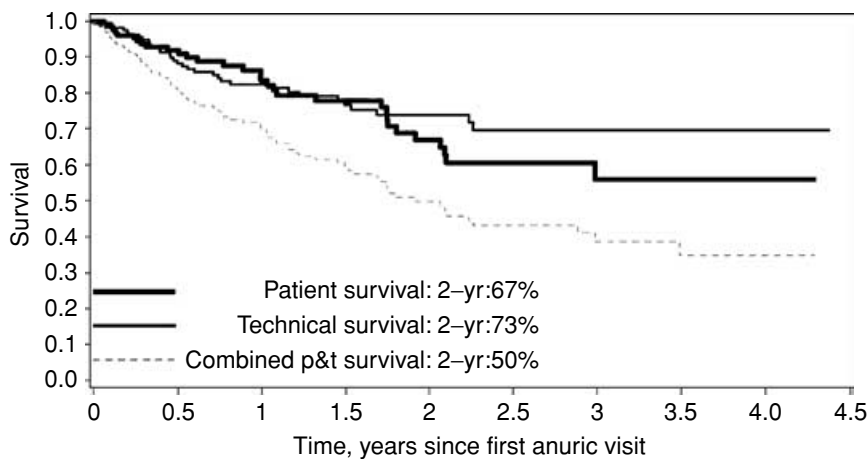


Fig. 1. Kaplan-Meier curves for the probability of patient survival (bold line), technique survival (normal line) and the combined patient and technique survival (dashed line). In the analyses for patient survival, the event is death, whereas transplantation, transfer to hemodialysis, and lost to follow-up are censored observations. In the analyses of technique survival the event is transfer to hemodialysis, while all other observations are censored. Both death and transfer to hemodialysis are events in the combined patient and technique survival curves.

Table 3. Multivariate Cox regression analysis of patient survival, technique survival, and combined patient and technique survival

	Patient survival (N = 130/32 events)			Technique survival (N = 130/26 events)			Combined patient and technique survival (N = 130/58 events)		
	RR	95% CI	P value	RR	95% CI	P value	RR	95% CI	P value
Age at entry years	1.08	1.04–1.12	<0.001				1.03	1.02–1.05	0.001
Davies score						NS			NS
Low	1			1					
Intermediate/high	3.83	1.19–12.4	0.02	0.40	0.17–0.93	0.03			
Subjective global assessment									
≤5	1.88	0.73–4.85	0.19	5.30	1.95–14.4	0.001	3.32	1.75–6.27	<0.001
6	0.49	0.15–1.60	0.23	2.14	0.75–6.06	0.15	1.15	0.55–2.40	0.7
7	1			1			1		
		P overall	0.08		P overall	0.004		P overall	<0.001
Time on dialysis									
<1½ years	0.36	0.15–0.89	0.03			NS	0.46	0.25–0.85	0.01
>1½ years	1						1		
Albumin g/dL	0.43	0.20–0.91	0.03			NS			NS
Hemoglobin g/dL	0.70	0.48–1.02	0.07			NS			NS
Membrane transport status			NS						NS
Slow/slow average				0.41	0.17–0.98	0.05			
Fast average/fast				1					

Table 4. Influence of clearance parameters on patient survival corrected for age, Davies score, subjective global assessment, time on dialysis, serum albumin, and hemoglobin concentration

		Kt/V _{urea} /week			Creatinine clearance L/week/1.73m ²				Ultrafiltration L/day					
		RR	95% CI	P value			RR	95% CI	P value			RR	95% CI	P value
Continuous Quintiles		0.43	0.11–1.66	0.22		0.96	0.92–1.00	0.08		0.48	0.23–0.97	0.04		
	<1.49	3.17	0.74–13.43	0.12	<41.3	2.71	0.79–9.25	0.11	<1.15	3.41	0.70–16.57	0.13		
	1.49–1.67	1.11	0.25–4.87	0.89	41.3–46.5	0.79	0.20–3.08	0.74	1.15–1.50	1.70	0.31–9.08	0.53		
	1.67–1.84	0.37	0.07–1.92	0.24	46.5–50.0	1.41	0.42–4.65	0.57	1.50–1.85	3.09	0.56–17.03	0.19		
	1.84–2.14	1.31	0.34–5.03	0.69	50.0–56.6	0.99	0.29–3.39	0.99	1.85–2.20	2.29	0.30–17.28	0.42		
	≥2.14	1		≥56.6	1			≥2.20	1					
			P overall	0.06			P overall	0.36			P overall	0.47		
Cutoff points	<1.7 (50)	1.47 (50)	0.70–3.12	0.31	<45 (29)	1.37	0.58–3.20	0.46	<1.25 (30)	2.29	0.82–6.38	0.11		
	≥1.7 (80)	1.00 (80)			≥45 (101)	1.00			≥1.25 (94)	1.00				
	<1.5 (15)	3.28 (15)	1.25–8.60	0.02	<40 (13)	3.26	1.24–8.55	0.02	<1.0 (14)	2.20	0.78–6.15	0.13		
	≥1.5 (115)	1 (115)			≥40 (117)	1			≥1.0 (110)	1				

The figures in parentheses give the number of patients per group.

1.7 per week to 2.0. It is evident, however, that mortality will be increased below a certain dose. The establishment of a lower adequacy limit can not be done in a randomized controlled trial because of obvious ethical reasons.

Therefore, carefully designed prospective controlled cohort studies with a wide variation in the prescribed dialysis dose are required. The NECOSAD cohort is such a study because measurements of renal function and

Table 5. Influence of clearance parameters on technique survival corrected for age, Davies score, subjective global assessment, time on dialysis, serum albumin, and hemoglobin concentration

	Kt/V _{urea} /week				Creatinine clearance L/week/1.73m ²				Ultrafiltration L/day			
	RR	95% CI	P value		RR	95% CI	P value		RR	95% CI	P value	
Continuous		1.51	0.43-5.33	0.52		1.02	0.99-1.04	0.12		1.13	0.59-2.14	0.70
Quintiles	<1.49	NA			<41.3	0.85	0.15-4.72	0.86	<1.15	0.61	0.17-2.19	0.45
	1.49-1.67	1.21	0.32-4.08	0.76	41.3-46.5	0.38	0.07-1.85	0.23	1.15-1.50	0.87	0.25-2.98	0.83
	1.67-1.84	1.08	0.31-3.80	0.89	46.5-50.0	0.74	0.20-2.63	0.64	1.50-1.85	1.38	0.46-4.14	0.56
	1.84-2.14	0.80	0.23-2.79	0.73	50.0-56.6	2.50	0.91-6.85	0.07	1.85-2.20	0.37	0.07-1.92	0.24
	≥2.14	1.00			≥56.6	1.00			≥2.20	1.00		
			P overall	0.96			P overall	0.08			P overall	0.48
Cutoff points	<1.7	1.22	0.55-2.70	0.62	<45	0.57	0.18-1.76	0.33	<1.25	0.45	0.15-1.36	0.16
	≥1.7	1.00			≥45	1.00			≥1.25	1.00		
	<1.5	NA			<40	1.03	0.21-4.93	0.96	<1.0	0.87	0.28-2.68	0.81
	≥1.5				≥40	1.00			≥1.0	1.00		

NA is not analyzed because of a small number of events.

dialysis dose are performed at 6-month intervals and the patients are well characterized with regard to comorbidity and nutritional status.

The present analysis in the NECOSAD cohort of patients who had become anuric during follow-up showed that patient and technique survival on peritoneal dialysis, mainly CAPD, was similar to the values reported by the EDTA/ERA for incident hemodialysis and peritoneal dialysis patients, the majority of them having residual renal function at the start of dialysis [27]. Patient survival in the anuric peritoneal dialysis patients was lower than that of all peritoneal dialysis patients included in NECOSAD [26]: 2-year survival 67% versus 84%. However, this can be explained by the duration of peritoneal dialysis prior to the outset of anuria. In the present study, duration of peritoneal dialysis of less than 1½ years prior to the onset of anuria was associated with a 64% reduction in the risk of death compared to a duration exceeding 1½ years. This is in accordance with our finding in the whole NECOSAD peritoneal dialysis population [26]. The recently published European APD Outcome Study (EAPOS) in anuric ambulatory peritoneal dialysis (APD) patients showed similar survival results, especially the combined 2-year patient and technique survival, which was almost identical [28]. These survival data do not support the fear that anuric peritoneal dialysis patients can often not be treated adequately with CAPD [29]. The values found for technique survival in the present study also make it unlikely that some, for instance, patients with a high body mass index, have been transferred to hemodialysis shortly after becoming anuric. Peritonitis, surgical complications, and “membrane failure,” including underdialysis and ultrafiltration failure, were the reported causes for transfer to hemodialysis. A surprising finding was the association between the presence of intermediate/high comorbidity and a high technique survival. The explanation is speculative, but one could assume that patients with a poor car-

diac condition were considered to be unfit for transfer to hemodialysis.

The well-known risk factors associated with decreased patient survival, such as age, comorbidity, nutritional status, and serum albumin, as reported in many studies, including the EAPOS [28], were also found in the anuric patients of the present study. In contrast to some other studies, peritoneal transport status was not associated with patient survival [30] or with the combined patient and technique survival [31]. However, a significant association with technique survival was present. A fast peritoneal transport status can lead to ultrafiltration failure and to a low Kt/V_{urea} [30]. Our data, therefore, suggest that the threshold to transfer these patients to hemodialysis was low.

None of the peritoneal solute transport parameters was significantly associated with patient survival when analyzed as continuous variables. However, normalized peritoneal creatinine clearance showed a tendency for an association between higher clearances and survival. The failure to reach statistical significance might have been due to a type II error, caused by the relatively low number of patients.

The analysis in quintiles showed an almost significant excess mortality for the group with the lowest Kt/V_{urea}. It can be seen from the extent of the clearance values that a wide range was present. This may explain the difference between our study and that of Szeto et al [21]. In the latter study from Hong Kong, the dialysis dose per patient was less flexible than in The Netherlands because of financial constraints. Also, the overall dose was lower and the patients transferred to hemodialysis were apparently not censored in the analysis of patient survival.

The use of various cutoff points enabled us to define the lowest adequacy limits below which mortality was significantly increased. These limits, Kt/V_{urea} <1.5/week, creatinine clearance <40 L/week/1.73 m², were markedly lower than generally assumed. This obviously does not

mean that they can be used directly in guidelines on the dialysis dose because a safety margin should always be present. However, these adequacy threshold levels suggest that a Kt/V_{urea} of 1.7/week and a creatinine clearance of at least 45 L/week are reasonable targets. It is also in line with the results of the ADEMEX Study showing that a further increase of these solute transport levels does not lead to better patient survival [19].

Anuric peritoneal dialysis patients are at risk for the development of overhydration, especially when they have ultrafiltration failure. Therefore peritoneal ultrafiltration was included as an adequacy parameter. A significant association was found with mortality in the time-dependent analysis. These findings are in line with those of the EA-POS where net ultrafiltration below 750 mL/24 hours predicted a higher mortality when compared to a volume above this value [28].

CONCLUSION

It can be concluded that anuric peritoneal dialysis patients have an acceptable patient and technique survival. The risk factors for death are the same as in the dialysis population as a whole. A peritoneal Kt/V_{urea} below 1.5/week, a creatinine clearance below 40 L/week/1.73 m², and a lower peritoneal ultrafiltration volume were all associated with an increased risk of death.

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